

Appendix G

2,908,693

PROCESS FOR THE PRODUCTION OF 2-METHYL
DIHYDROTESTOSTERONE

Howard J. Ringold and George Rosenthal, Mexico City, Mexico, assignors to Syntex S.A., Mexico City, Mexico, a corporation of Mexico

No Drawing. Application December 16, 1957
Serial No. 762,760Claims priority, application Mexico December 17, 1956
4 Claims. (Cl. 268—397.4)

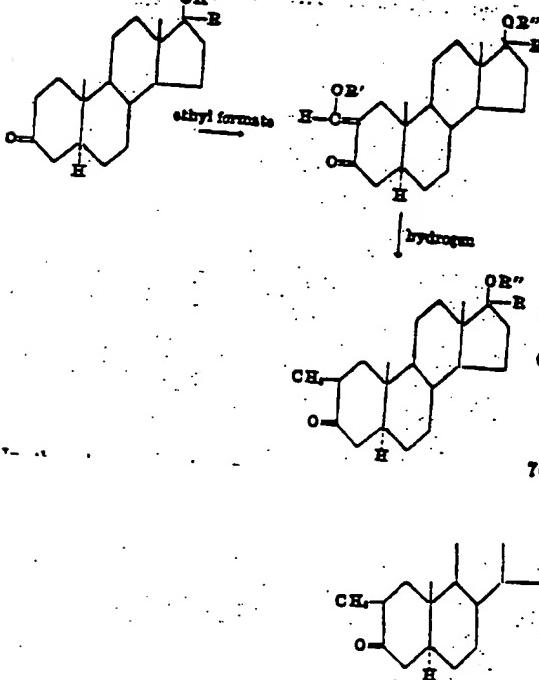
The present invention relates to a novel process for the production of cyclopentanophenanthrene derivatives.

More particularly the present invention relates to a process for the production of 2-methyl dihydrotestosterone derivatives and esters thereof as well as 2-methyl dihydrotestosterone derivatives having a C-17 lower alkyl group. The products of the process of the present invention have a useful high anabolic-androgenic ratio and are especially valuable for treatment of those ailments where an anabolic or antiestrogenic effect together with a lesser androgenic effect is desired.

In our U.S. application Serial No. 636,860, filed January 29, 1957, there is disclosed a process for the production of 2-methyl androstan compounds having a C-17 lower alkyl group involving preparing the corresponding 2-hydroxymethylene derivatives, transformation of these derivatives into 2-methyl-2-formyl compounds and removal of carbon monoxide to prepare the 2-methyl product.

In accordance with the present invention it has been discovered that 2-methyl androstan compounds or dihydrotestosterone derivatives may be prepared by a simple one step process involving catalytic hydrogenation of the corresponding 2-hydroxymethylene starting material. In its more specific aspects the process therefore involves treating dihydrotestosterone or a 17-lower alkyl dihydrotestosterone as with ethyl formate and sodium hydride to form the corresponding 2-hydroxymethylene derivative and catalytically hydrogenating the 2-hydroxymethylene derivative. Further it has been discovered that catalytic hydrogenation of a 2-acyloxymethylene derivative also produces the desired 2-methyl compounds.

The process of the present invention may therefore be illustrated by the following equation:



atoms such as methyl, ethyl or propyl. R' representing an acyl group of a hydrocarbon carboxylic acid of 2 to 12 carbon atoms as conventional to esterified steroid alcohols such as acetyl, propionyl, benzoyl etc. or R' represents hydrogen. R'' represents hydrogen when R is a lower alkyl group and is either hydrogen or an acyl group similar to R' when X is hydrogen.

In practicing the process as outlined above, dihydrotestosterone, or a 17-lower alkyl dihydrotestosterone, such as 17-methyl dihydrotestosterone or 17-ethyl dihydrotestosterone (which may be prepared by treatment of the known testosterone, 17-methyl testosterone or 17-ethyl testosterone with an alkali metal in liquid ammonia for example) are suspended in an inert organic solvent such as benzene and then mixed with ethyl formate and sodium hydride. The mixture is then stirred for a period of time of the order of 5 hours at room temperature and under nitrogen atmosphere. The suspension is then filtered and the mixture of the sodium salt of the desired hydroxymethylene compound is then treated with acid such as hydrochloric acid to precipitate the hydroxymethylene compound.

The hydroxymethylene compound thus prepared may then be conventionally purified to form a diester of a conventional type as previously set forth when the 17-hydroxy group of the starting compound is secondary or a monoster if the 17-hydroxy group is tertiary (as in 17-lower alkyl derivatives). The hydroxymethylene compound or the ester thereof in organic solvent solution is then hydrogenated in the presence of a hydrogenation catalyst preferably at room temperature and atmospheric pressure until absorption of hydrogen ceased.

Suitable organic solvents for the hydrogenation step are for example lower aliphatic alcohols such as methanol, ethyl acetate, dioxane or acetic acid. Preferable hydrogenation catalysts are palladium or platinum catalysts such as palladium on charcoal or palladium on barium sulfate or platinum oxide. This hydrogenation step produces the corresponding 2-methyl compound from either the ester of or the free hydroxymethylene compound and leaves any 17-ester group intact. The resultant crude 2-methyl products were then purified by chromatography. Where the free hydroxymethylene derivatives were being treated or when a free 2-methyl product was desired it was found desirable to treat the crude hydrogenation product with alkali prior to chromatography.

The following specific examples serve to illustrate but are not intended to limit the present invention.

Example I

A suspension of 10 g. of dihydrotestosterone in 500 cc. of anhydrous benzene free of thiophene was mixed with 10 cc. of ethyl formate and 3 g. of sodium hydride and the mixture was stirred for 5 hours under an atmosphere of nitrogen and at a temperature of approximately 25° C. The resulting suspension was filtered, the resulting mixture of the sodium salt of the hydroxymethylene compound and the excess of sodium hydride was washed with benzene and dried. This mixture was slowly added to a vigorously stirred solution of 20 cc. of concentrated hydrochloric acid in 500 cc. of water, and the stirring was continued for 30 minutes at the end of which the precipitate was collected and well washed with distilled water. After drying in vacuo, there was obtained 9.7 g. of 2-hydroxymethylene-dihydrotestosterone. 7 g. of 2-hydroxymethylene-dihydrotestosterone was dissolved in 300 cc. of methanol and mixed with 2.5% of a 10% palladium on charcoal catalyst. The mixture was hydrogenated at approximately 25° C. at atmospheric pressure until the absorption of hydrogen ceased.

In the above equation R represents hydrogen or R represents a lower alkyl group of less than 7 carbon atoms such as methyl, ethyl or propyl. R' representing an acyl group of a hydrocarbon carboxylic acid of 2 to 12 carbon atoms as conventional to esterified steroid alcohols such as acetyl, propionyl, benzoyl etc. or R' represents hydrogen. R'' represents hydrogen when R is a lower alkyl group and is either hydrogen or an acyl group similar to R' when X is hydrogen.

5

10

15

20

25

30

35

40

45

50

55

60

65

70

75

80

85

90

95

100

105

110

115

120

125

130

135

140

145

150

155

160

165

170

175

180

185

190

195

200

205

210

215

220

225

230

235

240

245

250

255

260

265

270

275

280

285

290

295

300

305

310

315

320

325

330

335

340

345

350

355

360

365

370

375

380

385

390

395

400

405

410

415

420

425

430

435

440

445

450

455

460

465

470

475

480

485

490

495

500

505

510

515

520

525

530

535

540

545

550

555

560

565

570

575

580

585

590

595

600

605

610

615

620

625

630

635

640

645

650

655

660

665

670

675

680

685

690

695

700

705

710

715

720

725

730

735

740

745

750

755

760

765

770

775

780

785

790

795

800

805

810

815

820

825

830

835

840

845

850

855

860

865

870

875

880

885

890

895

900

905

910

915

920

925

930

935

940

945

950

955

960

965

970

975

980

985

990

995

1000

1005

1010

1015

1020

1025

1030

1035

1040

1045

1050

1055

1060

1065

1070

1075

1080

1085

1090

1095

1100

1105

1110

1115

1120

1125

1130

1135

1140

1145

1150

1155

1160

1165

1170

1175

1180

1185

1190

1195

1200

1205

1210

1215

1220

1225

1230

1235

1240

1245

1250

1255

1260

1265

1270

1275

1280

1285

1290

1295

1300

1305

1310

1315

1320

1325

1330

1335

1340

1345

1350

1355

1360

1365

1370

1375

1380

1385

1390

1395

1400

1405

1410

1415

1420

1425

1430

1435

1440

1445

1450

1455

1460

1465

1470

1475

1480

1485

1490

1495

1500

1505

1510

1515

1520

1525

1530

1535

1540

1545

1550

1555

1560

1565

1570

1575

1580

1585

1590

1595

1600

1605

1610

1615

1620

1625

1630

1635

1640

1645

1650

1655

1660

1665

1670

1675

1680

1685

1690

1695

1700

1705

1710

1715

1720

1725

1730

1735

1740

1745

1750

1755

1760

1765

1770

1775

1780

1785

1790

1795

1800

1805

1810

1815

1820

1825

1830

1835

1840

1845

1850

1855

1860

1865

1870

1875

1880

1885

1890

1895

1900

1905

1910

1915

1920

1925

1930

1935

1940

1945

1950

1955

1960

1965

1970

1975

1980

1985

1990

1995

2000

2005

2010

2015

2020

2025

2030

2035

2040

2045

2050

2055

2060

2065

2070

2075

2080

2085

2090

2095

2100

2105

2110

2115

2120

2125

2130

2135

2140

2145

2150

2155

2160

2165

2170

2175

2180

2185

2190

2195

2200

2205

2210

2215

2220

2225

2230

2235

2240

2245

2250

2255

2260

2265

2270

2275

2280

2285

2290

2295

2300

2305

2310

2315

2320

2325

2330

2335

2340

2345

2350

2355

2360

2365

2370

2375

2380

2385

2390

2395

2400

2405

2410

2415

2420

2425

2430

2435

2440

2445

2450

2455

2460

2465

2470

2475

2480

2485

2490

2495

2500

2505

2510

2515

2520

2525

2530

2535

2540

2545

2550

2555

2560

2565

2570

2575

2580

2585

2590

2595

2600

2605

2610

2615

2620

2625

2630

2635

2640

2645

2650

2655

2660

2665

2670

2675

2680

2685

2690

2695

2700

2705

2710

2715

2720

2725

2730

2735

2740

2745

2750

2755

2760

2765

2770

2775

2780

2785

2790

2795

2800

2805

2810

2815

2820

2825

2830

2835

2840

2845

2850

2855

2860

2865

2870

2875

2880

2885

2890

2895

2900

2905

2910

2915

2920

2925

2930

2935

2940

2945

2950

2955

2960

2965

2970

2975

2980

2985

2990

2995

3000

3005

3010

3015

3020

3025

3030

3035

3040

3045

3050

3055

3060

3065

3070

3075

3080

3085

3090

3095

3100

3105

3110

3115

3120

3125

3130

3135

3140

3145

3150

3155

3160

3165

3170

3175

3180

3185

3190

3195

3200

3205

3210

3215

3220

3225

3230

3235

3240

3245

3250

3255

3260

3265

3270

3275

3280

3285

3290

3295

3300

3305

3310

3315

3320

3325

3330

3335

3340

3345

3350

3355

3360

3365

3370

3375

3380

3385

3390

3395

3400

3405

3410

3415

3420

3425

3430

3435

3440

3445

3450

3455

3460

3465

3470

3475

3480

3485

3490

3495

3500

3505

3510

3515

3520

3525

3530

3535

3540

3545

3550

3555

3560

3565

3570

3575

3580

3585

3590

3595

3600

3605

3610

3615

3620

3625

3630

3635

3640

3645

3650

3655

3660

3665

3670

3675

3680

3685

3690

3695

3700

3705

3710

3715

3720

3725

3730

3735

3740

3745

3750

3755

3760

3765

3770

3775

3780

3785

3790

3795

3800

3805

3810

3815

3820

3825

3830

3835

3840

3845

3850

3855

3860

3865

3870

3875

3880

3885

3890

3895

3900

3905

3910

3915

3920

3925

3930

3935

3940

3945

3950

3955

3960

3965

3970

3975

3980

3985

3990

3995

4000

4005

4010

4015

4020

4025

4030

4035

4040

4045

4050

4055

4060

4065

4070

4075

4080

4085

4090

4095

4100

4105

4110

4115

4120

4125

4130

4135

4140

4145

4150

4155

4160

4165

4170

4175

4180

4185

4190

4195

4200

4205

4210

4215

4220

4225

4230

4235

4240

4245

4250

4255

4260

4265

4270

4275

4280

4285

4290

4295

4300

4305

4310

4315

4320

4325

4330

4335

4340

4345

4350

4355

4360

4365

4370

4375

4380

4385

4390

4395

4400

4405

4410

4415

4420

4425

4430

4435

4440

4445

4450

4455

4460

4465

4470

4475

4480

4485

4490

4495

4500

4505

4510

4515

4520

4525

4530

4535

4540

4545

4550

4555

4560

4565

4570

4575

4580

4585

4590

4595

4600

4605

4610

4615

4620

4625

4630

4635

4640

4645

4650

4655

4660

4665

4670

4675

4680

4685

4690

4695

4700

4705

4710

4715

4720

4725

4730

4735

4740

4745

4750

4755

4760

4765

4770

4775

4780

4785

4790

4795

4800

4805

4810

4815

4820

4825

4830

4835

4840

4845

4850

4855

4860

4865

4870

4875

4880

4885

4890

4895

4900

4905

4910

4915

4920

4925

4930

4935

4940

4945

4950

4955

4960

4965

4970

4975

4980

4985

4990

4995

5000

5005

5010

5015

5020

5025

5030

5035

5040

5045

5050

5055

5060

5065

5070

5075

5080

5085

5090

5095

5100

5105

5110

5115

5120

5125

In the above equation R represents hydrogen or R represents a lower alkyl group of less than 7 carbon

catalyst was removed by filtration, 1 g. of potassium hydroxide in 5 cc. of water was added to the solution which

2,908,693

3

was then kept for 1 hour at room temperature. 2 cc. of acetic acid was added, the solvent was completely removed under reduced pressure, water was added to the residue, and the product was extracted with methylene dichloride. The extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. The residue was dissolved in benzene and transferred to a chromatographic column with 125 g. of alkaline alumina. The column was washed with successive fractions of 100 cc. of benzene, whereupon the desired product was eluted from fractions 2 to 6. After evaporating the solvent, the product was crystallized from a mixture acetone-hexane to yield 3.3 g. of pure 2 α -methyl-dihydrotestosterone.

Example II

2 g. of 2-hydroxymethylene-dihydrotestosterone, obtained in accordance with Example I, dissolved in 80 cc. of acetic acid was hydrogenated with 1.0 g. of 10% palladium on charcoal catalyst under the conditions described in the previous example. After removing the catalyst by filtration, the solvent was evaporated to dryness under reduced pressure and the residue was mixed with 100 cc. of methanol and 1 g. of potassium hydroxide. The solution was refluxed for 30 minutes and then diluted with water and extracted with methylene dichloride. The extract was washed with water to neutral, dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. The residue was dissolved in benzene and chromatographed under the conditions described in Example I. There was thus obtained 2 α -methyl-dihydrotestosterone.

Example III

A mixture of 1 g. of 2-hydroxymethylene-dihydrotestosterone, obtained in accordance with the method described in Example I, 10 cc. of pyridine and 2 cc. of acetic anhydride was allowed to react at room temperature for 16 hours and then poured into water. The product was extracted with methylene dichloride and washed consecutively with dilute hydrochloric acid, sodium bicarbonate solution and water, dried and evaporated to dryness under reduced pressure. There was thus obtained the diacetate of 2-hydroxymethylene-dihydrotestosterone.

This diacetate was hydrogenated and then worked up by the methods described in the previous examples, thus producing 2 α -methyl-dihydrotestosterone, identical to the one obtained in accordance with such examples.

Example IV

Following the method described in the previous examples, 17 α -methyl-dihydrotestosterone was converted into 2 α ,17 α -dimethyl-dihydrotestosterone.

4

Example V

Following the method described in Examples I, II, and III, 17 α -ethyl-dihydrotestosterone was converted into 2 α -methyl-17 α -ethyl-dihydrotestosterone.

Example VI

A mixture of 1 g. of 2-hydroxymethylene-dihydrotestosterone, obtained in accordance with Example I, 10 cc. of pyridine and 2 cc. of propionic anhydride was allowed to react at room temperature for 16 hours and then poured into water. The resulting suspension was heated for 1 hour on the steam bath to hydrolyze the excess of propionic anhydride, cooled and extracted with methylene dichloride. The extract was consecutively washed with dilute hydrochloric acid, sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. There was thus obtained the dipropionate of 2-hydroxymethylene-dihydrotestosterone which was treated with hydrogen, in methanol solution, under the conditions described in Example I. When the uptake of hydrogen ceased, the catalyst was filtered and the solution was evaporated to dryness under vacuum. The residue was dissolved in a mixture benzene-hexane, transferred to a chromatographic column with neutral alumina and the product was eluted with mixtures benzene-hexane, gradually increasing the proportion of benzene in the mixture. Crystallization of the eluates from acetone-hexane yielded the propionate of 2 α -methyl-dihydrotestosterone.

We claim:

1. A process for the production of compounds selected from the class consisting of 2 α -methyl dihydrotestosterone, 17 α -esters thereof of hydrocarbon carboxylic acids of 2 to 12 carbon atoms and 2 α -methyl 17 α -lower alkyl dihydrotestosterone comprising hydrogenating the corresponding 2-hydroxymethylene derivatives in the presence of a hydrogenation catalyst selected from the group consisting of palladium and platinum catalyst.
2. The process of claim 1 wherein the starting material is a diester of 2-hydroxymethylene dihydrotestosterone and the product is a 17 α -ester of 2 α -methyl dihydrotestosterone.
3. The process of claim 1 wherein the starting material is 2-hydroxymethylene dihydrotestosterone and the product is 2 α -methyl dihydrotestosterone.
4. The process of claim 1 wherein the starting material is a 17 α -lower alkyl 2-hydroxymethylene dihydrotestosterone and the product is a 17 α -lower alkyl 2 α -methyl dihydrotestosterone.

References Cited in the file of this patent

Hogg: J. A. C. S., December 5, 1955, pages 6401-6402.